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(54) Title: PARAMETRIC CONTROL IN PULSED LIGHT STERILIZATION OF PACKAGES AND THEIR CONTENTS (57) Abstract <p>An approach for sterilizing microorganisms at a target object employs a flashlamp system including means for generating pulses of light, and for deactivating microorganisms within the target object by illuminating the target object with the pulses of light having been generated; a photo-sensitive detector positioned so as to receive a portion of each of the pulses of light as a measure of an amount of light illuminating the target object, for generating an output signal in response thereto; and a control system, coupled to the flashlamp system and the photo-sensitive detector, for determining, in response to the output signal, whether the pulses of light are sufficient to effect a prescribed level of deactivation of microorganisms in the target object. In accordance with this approach sterilizing microorganisms involves steps of generating a pulse of light; deactivating microorganisms at the target object by directing the pulse of light having been generated at the target object; receiving a portion of the pulse of light as a measure of an amount of the pulse of light illuminating the target object; generating an output signal in response to the receiving of the portion of the pulse of light; and determining, in response to the generating of the output signal, whether the pulse of light is sufficient to effect a prescribed level of deactivation of microorganisms in the target object.</p>		

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**PARAMETRIC CONTROL IN PULSED LIGHT
STERILIZATION OF PACKAGES AND THEIR CONTENTS**

BACKGROUND OF THE INVENTION

The present invention relates to deactivation
10 of microorganisms, and more particularly to parametric
control in the deactivation of microorganisms using
pulsed light. More particularly, the present invention
relates to parametric control in the deactivation of
microorganisms on packages or their contents using high-
15 intensity, short-duration pulses of incoherent,
polychromatic light in a broad spectrum. Even more
particularly, the present invention relates to monitoring
and controlling key pulsed light parameters in the
deactivation of microorganisms on packages or their
20 contents using high-intensity, short-duration pulses of
incoherent, polychromatic light in a broad spectrum to
verify sterilization has been achieved.

Polyvinyl Chloride (PVC) is a standard, widely
used plastic packaging material used to manufacture
25 flexible containers (bags and pouches) for the
administration of small volume parenterals (SVPs), often
referred to as mini-bags; large volume parenterals
(LVPs); and various enteral nutritional and liquid
preparations. These containers are often utilized for
30 patient hydration and/or to supply pharmaceutical
preparations, medicines, vitamins, nutritionals, and the
like. Heretofore, PVC has proven to be advantageous
because of its resistance to heat, which allows the
containers to be terminally sterilized using high
35 temperature treatment, i.e., sterilized after filling to
deactivate microorganisms inside the containers,

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including microorganisms suspended in liquid content of the container, using high temperature treatment (e.g., autoclaving).

In many cases, an overwrap is also used to help
5 the flexible containers to survive autoclaving (i.e., high temperature treatment), and also to increase the shelf life of parenteral fluids contained therein by providing improved moisture vapor barrier (MVB) properties, as compared to the MVB properties of PVC
10 alone. In many cases, and particularly for SVP packages (or bags), multiple SVP packages are placed into one overwrap package. Disadvantageously, once the one overwrap package has been opened, the shelf life of the individual SVP packages contained therein is limited to
15 approximately 30 days, because of the poor MVB properties of PVC. Thus, if a practitioner opens an overwrap containing SVPs, but does not use all of the SVPs in a timely manner, the SVP packages must be discarded approximately 30 days after the overwrap is opened. The
20 overwrap also represents a significant added packaging cost and contributes to environmental waste.

Using materials other than PVC, such as Olefins (e.g., Polyethylene or Polypropylene); nylon, or a composite material, either laminated or co-extruded
25 structure (including both monolayer and multilayer structures), and the like, for SVP and/or LVP packages offers a number of significant advantages. One advantage is to reduce or eliminate the use of PVC because of environmental concerns. Another advantage of materials
30 such as polyethylene is that they have much better MVB properties than PVC. For example, in some instances, it may be possible to achieve a longer shelf life (for example, 24 months versus the 15 to 18 months achievable with PVC and overwrap) without the inconvenience and
35 added cost of the overwrap.

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Another advantage to replacing PVC with a material such as polyethylene is that products such as pure deionized water (U.S.P. for injection) cannot be effectively packaged in PVC because by-products from the
5 PVC packaging material leach into the pure deionized water, contaminating it, whereas materials such as polyethylene can be formulated so as not to contain by-products that leach into the pure deionized water.

Enteral pre-filled packages also benefit in
10 these ways.

Empty parenteral and enteral containers are also widely used, with liquid contents typically being manually added after delivery of the containers by a pharmacist or dietitian. These empty containers,
15 heretofore typically produced in PVC, are often terminally sterilized using autoclaving. Unfortunately, these empty containers also suffer from the problems described above.

Thus, advantages exist to using olefin, nylon
20 and composite material containers.

However, heretofore known methods of terminal sterilization, such as autoclaving, are unsuitable for use with polyethylene containers or thin polypropylene containers, because such containers are unable to
25 withstand the temperatures (e.g., between 100 and 200 °C) or pressures of autoclaving. (Polypropylene containers are able to withstand some amount of commercially useful autoclaving, however, are required to be thicker and more expensive to withstand autoclaving than would need be in
30 the absence of this high heat and pressure treatment.) Thus, there exists a need for an approach to deactivating microorganisms in a container that does not require the use of heat that may damage the container or its contents.

35 Other processes, such as the process suggested by Beigler, et al. in the United States Patent No.

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4,282,863, entitled METHODS OF PREPARING AND USING INTRAVENOUS NUTRIENT COMPOSITIONS, issued August 11, 1981, employ gamma radiation to achieve terminal sterilization. Unfortunately, the use of gamma radiation
5 creates other problems. For example, gamma radiation is prone to altering the polymeric structure of the olefin container (i.e., gamma radiation degrades the product container integrity), which can result in weakened container integrity, leakage, increased gas permeability
10 and other such problems. Also gamma radiation can attack the package and/or its contents to produce other adverse changes, such as darkening, off-colors or color changes, etc. in the package or its contents. Furthermore, gamma radiation inherently causes the generation of highly
15 reactive species, such as hydroxyl radicals produced during the gamma radiation of water, that may detrimentally alter the chemical structure of the product being treated. Thus, there exists a need for an improved sterilization process usable with polyolefins and the
20 like that does not employ gamma radiation, or other such reactive processes, to achieve sterilization.

Other problems with heat treatment, i.e., autoclaving, and heretofore employed gamma radiation treatment techniques include the "batch" nature of such
25 processes. Specifically, with heat or gamma radiation treatment, product containers are treated in groups or batches, which problematically requires additional handling of the product not required if an on-line continuous process is used. In addition, careful
30 inventorying and product handling are required in order to assure that each batch is segregated, and separately treated and tested.

In addition, with heretofore employed terminal sterilization techniques it is nearly impossible to
35 monitor all of the parameters necessary to assure adequate deactivation of microorganisms in all of the

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product packages in a given batch (i.e., parametric control is nearly impossible). (For example, it is difficult to monitor the temperature within the autoclave at enough points than one can assure that every part of every package in the batch received enough heat and saturated steam pressure to achieve adequate deactivation of microorganisms.) Because such parametric control is not generally possible with heretofore employed terminal sterilization techniques, such containers must be observed after, e.g., a fourteen day period following terminal sterilization to determine whether any contaminants are present in selected (or all) containers from each batch. This unfortunately further complicates product and product container treatment and delays usage of the packages and products having been treated. An approach that can be performed in a continuous manner, e.g., as a part of a packaging process, thus eliminating the need for "batch" handling and "batch" testing; and an approach that allows adequate parametric control over processing parameters needed to assure adequate sterility levels, thus eliminating the need for an observation period following treatment, would be highly advantageous.

It is generally accepted that terminally sterilized articles for medical or food applications, when processed, for example, in an autoclave, must attain greater than a 10^{-6} survivor probability among microbial contaminants. In other words, there must be less than once chance in a million that viable microorganisms are present in a sterilized article. This level of sterilization is referred to as a sterility assurance level of 10^{-6} .

Another approach to sterilization of parenteral and enteral containers involves presterilizing the containers using, for example, autoclaving, gamma radiation, chemical treatments or the like, and then filling such containers in an aseptic environment. A

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sterility assurance level of 10^{-6} is needed for most parenteral and enteral applications, and is difficult to verify using heretofore known aseptic filling approaches. (Current aseptic processes are validatable at sterility
5 confidence levels of more than approximately 10^{-3} by the use of media fills to demonstrate the absence of growth potential.) Thus, the U.S. Food and Drug administration, for example, has stated its preference for terminal sterilization processes, even though it recognizes that
10 many products and product packages are damaged by such processes.

Therefore, what is needed is an approach to deactivating microorganisms in a container that achieves an easily verifiable sterility assurance level of at
15 least, for example, 10^{-6} , but reduces product and product container damage, such as can occur with current terminal sterilization techniques, such as autoclaving or gamma radiation treatment.

The present invention advantageously addresses
20 the above and other needs.

SUMMARY OF THE INVENTION

The present invention advantageously addresses the needs above as well as other needs by providing an
25 approach for deactivating microorganisms, and more particularly for the deactivating of microorganisms within parenteral and/or enteral solutions and packages or containers or contact lens solutions and packages and/or ophthalmic solutions and packages, and within
30 product contents of such packages, using high-intensity, short-duration pulses of incoherent, polychromatic light in a broad spectrum directed at the packages, filled and/or empty, so as to penetrate the packages and deactivate microorganisms on an interior surface thereof
35 and/or suspended within the volume or product contained within the packages.

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In one embodiment, the invention can be characterized as an apparatus for sterilizing microorganisms in a container. Such apparatus employs the container, which includes a polyolefin, and which
5 transmits light in a spectrum containing wavelengths selected from between 120 nm and 2600 nm, e.g., wavelengths between 180 nm and 1500 nm or, e.g., between 180 nm and 300 nm. The container is coupled to a port through which a product within the container can be
10 withdrawn. The port may be, for example, a plastic tube or cap having a puncture site at which it is designed to be punctured for administration of its contents, or may be a cap that is unscrewed or otherwise removed before administration. Such ports are well known in the art.

15 A flashlamp system generates high-intensity, short-duration pulses of polychromatic light in a broad spectrum, and the pulses of light generated by the flashlamp illuminate the container and deactivate microorganisms within the container.

20 In a variation of this embodiment, an interface region at which the port is bonded to the container is also illuminated and microorganisms within the port and at the interface region are deactivated by the high-intensity, short-duration pulses of incoherent,
25 polychromatic light in a broad spectrum.

In another embodiment, the invention may be characterized as an apparatus for deactivating microorganisms in a container that employs the container, which, in this embodiment, contains a transmissive
30 product that transmits more than about one percent of light at a wavelength of 260 nm, and which container transmits light in a spectrum having wavelengths selected from between 120 nm and 2600 nm (see examples above). The embodiment also employs a port coupled to the container
35 through which the product within the container can be withdrawn, and a flashlamp system that generates high-

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intensity, short-duration pulses of polychromatic light in a broad spectrum, and deactivates microorganisms within the container by illuminating the container with such pulses of light.

5 In a further embodiment, the invention can be characterized as an apparatus for deactivating microorganisms in a container. The apparatus of this embodiment employs the container, which in this
10 embodiment transmits light in a spectrum including wavelengths selected from between 120 nm and 2600 nm (see examples above); and a port coupled to the container through which a product within the container can be withdrawn; and a flashlamp system that generates high-intensity, short-duration pulses of polychromatic light
15 in a broad spectrum, and deactivates microorganisms within the container and port by illuminating the container and port with the pulses of light.

 In an additional embodiment, the invention can be characterized as an apparatus for deactivating
20 microorganisms in a container employing the container, which includes at least one port through which the product within the container can be withdrawn, and transmits light in a spectrum having wavelengths selected from between 120 nm and 2600 nm (see examples above); a
25 flashlamp system that generates high-intensity, short-duration pulses of polychromatic light in a broad spectrum, and deactivates microorganisms within the container by illuminating the container with the pulses of light having been generated. The flashlamp of this
30 embodiment advantageously deactivates sufficient microorganisms to achieve a sterility assurance level of at least 10^{-6} .

 In yet another embodiment, the invention can be characterized as an apparatus for sterilizing
35 microorganisms in a container. The container of such embodiment includes a blister formed therein, and a

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backing material that together with the blister forms a cavity in which is contained a contact lens and a preservative fluid. The preservative fluid is at least one percent transmissive to light having a wavelength of 260 nm. A flashlamp system generates high-intensity, short-duration pulses of polychromatic light in a broad spectrum that deactivate microorganisms within the container by illuminating the container with the pulses of light having been generated.

10 In an even further embodiment, the present invention can be characterized as an apparatus for sterilizing microorganisms at a target object. Such apparatus employs a flashlamp system including means for generating high-intensity, short-duration pulses of polychromatic light in a broad spectrum, and for 15 deactivating microorganisms within the target object by illuminating the target object with the pulses of light having been generated; a photo-sensitive detector positioned so as to receive a portion of each of the pulses of light as a measure of an amount of light 20 illuminating the target object, for generating an output signal in response thereto; and a control system, coupled to the flashlamp system and the photo-sensitive detector, for determining, in response to the output signal, 25 whether the pulses of light are sufficient to effect a prescribed level of deactivation of microorganisms in the target object.

In still a further embodiment, the present invention can be characterized as a method for 30 sterilizing microorganisms in a target object, having steps of generating a high-intensity, short-duration pulse of polychromatic light in a broad spectrum; deactivating microorganisms at the target object by directing the pulse of light having been generated at the 35 target object; receiving a portion of the pulse of light as a measure of an amount of the pulse of light

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illuminating the target object; generating an output
signal in response to the receiving of the portion of the
pulse of light; and determining, in response to the
generating of the output signal, whether the pulse of
5 light is sufficient to effect a prescribed level of
deactivation of microorganisms in the target object.

BRIEF DESCRIPTION OF THE DRAWINGS

The above and other aspects, features and
10 advantages of the present invention will be more apparent
from the following more particular description thereof,
presented in conjunction with the following drawings
wherein:

FIG. 1 is a schematic diagram of an apparatus
15 for fabricating, filling, sealing and sterilizing a
parenteral or enteral package;

FIG. 2 is a side view diagram of an exemplary
parenteral package suitable for use in a sterilizing
chamber (or tunnel) of the apparatus of FIG. 1;

20 FIG. 2A is a perspective view of another
exemplary parenteral package suitable for use in a
sterilizing chamber (or tunnel) of the apparatus of
FIG. 1;

FIG. 3 is a top view of a contact lens package,
25 having a "hemispherical" blister, and being suitable for
use in the sterilizing chamber (or tunnel) of the
apparatus of FIG. 1;

FIG. 4 is a side view of the contact lens
package of FIG. 3, being suitable for use in the
30 sterilizing chamber (or tunnel) of the apparatus of
FIG. 1;

FIG. 5 is a top view of a contact lens package,
having a "rectangular" blister, and being suitable for
use in the sterilizing chamber (or tunnel) of the
35 apparatus of FIG. 1;

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FIG. 6 is a side view of the contact lens package of FIG. 5, being suitable for use in the sterilizing chamber (or tunnel) of the apparatus of FIG. 1;

5 FIG. 7 is an end view of the parenteral package of FIG. 2 and one variation of a sterilizing chamber of the apparatus of FIG. 1;

 FIG. 8 is an end view of the parenteral package of FIG. 2 and another variation of the sterilizing
10 chamber (or tunnel) of the apparatus of FIG. 1;

 FIG. 9 is a perspective view of a sterilizing chamber, such as the sterilizing chamber of FIG. 7, wherein a photodetector is used to measure the character of the treatment light, such as fluence per flash, in
15 order to maintain parametric control over sterilization of packages and their contents in such sterilization chamber;

 FIG. 10 is a perspective view of several parenteral packages, a further variation of the
20 sterilization chamber (or tunnel) of the apparatus of FIG 1, and a transport approach for moving the parenteral packages through the sterilization chamber;

 FIG. 11 is a perspective view of several blow-fill-seal containers on several cards, an additional
25 variation of the sterilization chamber (or tunnel) of the apparatus of FIG. 1, and a transport approach for moving the cards through the sterilization chamber; and

 FIG. 12 is a perspective view of several enteral packages, a further additional variation of the
30 sterilization chamber of the apparatus of FIG 1, and a transport approach for moving the enteral packages through the sterilization chamber.

 Corresponding reference characters indicate corresponding components throughout the several views of
35 the drawings.

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DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following description of the presently contemplated best mode of practicing the invention is not to be taken in a limiting sense, but is made merely for the purpose of describing the general principles of the invention. The scope of the invention should be determined with reference to the claims.

Referring first to FIG. 1, the diagram of an apparatus 10 for fabricating, filling, sealing, and sterilizing a parenteral or enteral package 12 is shown. A roll 14 (or other supply) of packing material is fed by, for example, rollers 15, into a fabricating, filling and sealing apparatus 16, such as are known in the art. Alternatively, the packaging material may assume a form of resin beads, as would be the case typically in a blow/fill/seal apparatus. The fabricating, filling and sealing apparatus 16 may be a form/fill/seal apparatus; a blow/fill/seal apparatus; an injection blow molding apparatus; an extrusion and coextrusion blow molding apparatus; a film/sheet extrusion and coextrusion apparatus; a thermoforming apparatus; or an injection molding apparatus, such as are known in the art. Various sealing equipment and techniques may be employed including heat sealing, radio frequency (RF) fabrication, hot plate welding, induction welding, and/or spin welding, all of which are well known in the art.

Also shown, is a treatment zone, or sterilization tunnel, 18 (sterilizing chamber 18) through which fabricated, filled and sealed parenteral or enteral packages are passed, by, for example, a conveyer belt 20, in order to sterilize such packages. The conveyer belt 20 may employ one or more quartz shelves on which the parenteral or enteral packages rest while they are conveyed, or one or more hooks from which the parenteral or enteral packages hang while they are conveyed or any of a number of other well known means of conveyance. In

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this way, the parenteral or enteral packages are not shielded from light as they pass through the sterilizing chamber 18.

The forming, filling and sealing apparatus 16 may, as mentioned above, be of a type well-known in the art, and preferably is capable of manufacturing containers (or packages) at high speeds, and with from one to multiple cavitations.

One example of a suitable blow/fill/seal apparatus adaptable for use with the present embodiment is marketed under Model No. 603 by Automatic Liquid Packaging, Inc. of Illinois. Another such apparatus is marketed under Model No. 624 by Automatic Liquid Packaging of Woodstock, Illinois.

A suitable form/fill/seal apparatus utilizes an extruded film to form a pouch or bag. One example of such a form/fill/seal apparatus adaptable for use with the present embodiment is marketed as System Model Mark III by Inpaco of Allentown, Pennsylvania.

Both the blow/fill/seal apparatuses and the form/fill/seal apparatuses mentioned above permit the attachment of fitments (see FIG's. 2 and 2A) during formation of the package or container.

The sterilizing chamber 18, as shown, may consist of one or more reflectors 22, and one or more flashlamps (not shown), such as are available as Part No. 01812-525 from PurePulse Technologies, Inc., of San Diego, California. Such flashlamps and attendant pulse-generating hardware (not shown) are capable of generating high-intensity, short-duration pulses of incoherent polychromatic light in broad spectrum. Suitable flashlamps and attendant pulse generating hardware are described in U.S. Patent No's. 4,871,559 (METHODS FOR PRESERVATION OF FOODSTUFFS); 4,910,942 (METHODS FOR ASEPTIC PACKAGING OF MEDICAL DEVICES); and 5,034,235 (METHODS FOR PRESERVATION OF FOODSTUFFS), issued to Dunn,

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et al. (the '559, '942 and '235 patents, respectively), incorporated herein by reference as if set forth in their entirety. As will be appreciated by the skilled artisan, numerous known and yet-to-be-developed variations of the flashlamps and pulse generating hardware are suitable for use in the embodiments disclosed herein.

The one or more reflectors 22 direct light from the flashlamps toward completed parenteral or enteral packages 12. Preferably, the reflectors 22 are made from, for example, aluminum, and optimally reflect light across the entire spectrum of light generated by the flashlamps. Advantageously, the reflectors may be designed, using commonly known design techniques, to create a uniform or non-uniform energy distribution of light across the parenteral or enteral package being illuminated. In this way, for example, greater amounts (i.e., concentrations) of light energy can be directed, for example, at thicker portions of the parenteral or enteral package, such as around an additive port and/or an administration port; and/or at portions of the product contained therein, such as near the middle of the parenteral or enteral package where a greater volume of product needing treatment may be present.

In accordance with the present embodiment, the pulses of light pass through the parenteral or enteral packages 12, reaching the contents of such packages, and effecting sterilization or deactivation of microorganisms at the interior of the packages 12 and suspended within products contained in the packages 12.

In this way, an effective method is provided for sterilizing, not only parenteral or enteral packages, but product contents thereof, without requiring the high temperature processes involved in autoclaving. In addition, other product containers and products contained therein may be treated using the approach of this embodiment. For example, contact lens packages and the

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contact lenses contained therein can be treated using the above-approach. As a result, materials such as Olefins, nylon, and composite materials may advantageously be employed in product packages, instead of more conventional materials, such as polyvinyl chloride (PVC). Because Olefins, nylon, and composite materials can have superior moisture vapor barrier characteristics to those of PVC, and may not contain components that are readily absorbed into the products contained therein, the above apparatus and attendant methods, provide a vastly superior forming, filling, sealing and sterilizing approach than has heretofore been available. Furthermore, the present embodiment achieves a sterility assurance level of at least 10^{-6} , and does not require the use of gamma radiation or other highly degradative processes.

Referring to FIG. 2, a typical small volume parenteral container 12 or large volume parenteral container 12 configuration is shown (generically referred to herein as a bag assembly 12). The bag assembly 12 employs a flexible pouch 30, made in the preferred embodiment from a polyolefin, such as polyethylene, to which a fitment 32 is joined. The fitment 32 generally includes two short tubes 36, 38 (or ports), through which a connection can be made for delivery of a liquid from the flexible pouch 30 (or parenteral pouch) to a feed tube (not shown), or to the flexible pouch, such as by a practitioner (often a pharmacist or nurse) when making an additive to the flexible pouch 30.

One port 36, the port used to make an additive, is typically referred to as an additive port 36, and another port 38, the port used for delivery of fluid, is typically referred to as an administration port 38. With a device referred to as an intravenous set (not shown), which is "spiked", i.e., punctured through, at the administration port 36, the flexible pouch's 30 contents

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can be delivered to a patient, either by gravity or with the use of a pump or controller (not shown).

Enteral containers (not shown), made preferably from polyolefins, such as polyethylene, utilize similar
5 fitments, however, an enteral set (or spike set) and flexible tubing used with the enteral container is typically used to deliver liquid to a patient's stomach by a variety of methods, such as through a gastronomy tube for, for example, liquid feeding.

10 The flexible pouch 30 is preferably constructed of materials that transmit light in a spectrum of from, for example, between 180 nm and 1500 nm. Many materials, such as Polyethylene, Polypropylene, EVOH, nylon and a number of other plastic materials, either monolayer or
15 multilayer, readily transmit this spectrum and can be used, in accordance with variations of the present embodiment.

The joining of the fitment 32 to the flexible pouch 30, and the filling of the flexible pouch 30, can
20 preferably be conducted in an aseptic environment, such as a HEPA-filtered chamber, in a packaging machine, to minimize introduction of contaminants, such as microorganisms. (Such HEPA-filtered chambers are well known in the art.) The fitment 32 can be joined to the
25 flexible pouch 30 by heat sealing, radio frequency (RF) welding or "plastic welding" techniques of the type commonly known in the art. An alternative example of a parenteral package suitable for use with the embodiment of FIG. 1 is shown in FIG. 2A.

30 Referring to FIG. 3, a top view is shown of a contact lens package 50, having a "hemispherical" blister 52, and being suitable for use in the sterilizing chamber (or tunnel). The contact lens package 50 has a polyolefin panel 54 (such as a polyethylene or polypropylene panel)
35 into which is formed the blister 52. The blister 52 protrudes from a top side 56 (FIG. 4) of the polyolefin

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panel 56, and a lid stock which may include foil backing 58 (FIG. 4) is adhered to the a bottom 60 of the polyolefin panel 54. Between the lid stock 58, and an interior of the blister 52 is formed a cavity 62 that is
5 filled with a preservative fluid, such as saline solution, and a contact lens 67, such as a soft contact lens.

High-intensity, short-duration pulses of incoherent polychromatic light 66 (FIG. 4) are in
10 practice directed at the top 56 of the polyolefin panel 54, and at the sides of the blister. The high-intensity, short-duration pulses of incoherent polychromatic light 66 (FIG. 4) have an intensity, duration, and wavelength or wavelengths as follows: intensity of from 0.01 J/cm² to
15 50 J/cm², e.g., 0.05 J/cm² to 5 J/cm², e.g., 2 J/cm²; duration of from 0.001 ms to 100 ms, e.g., 0.3 ms; and wavelengths selected from between 120 nm and 2600 nm, e.g., wavelengths between 180 nm and 1500 nm or, e.g., between 180 nm and 300 nm. The high-intensity, short-
20 duration pulses of incoherent polychromatic light 66 (FIG. 4) penetrate the blister 52, which is substantially transparent to light having wavelengths in the range selected, and impinge upon the preservative fluid and contact lens 64 contained therein. As a result,
25 microorganisms at the interior of the blister 52, suspended in the preservative solution, and on or in the contact lens 64 are deactivated.

Advantageously, the contact lens 64 is sealed within the polyolefin package 50 prior to illumination of
30 the package 50 with the high-intensity, short-duration pulses of incoherent polychromatic light, therefore preventing contamination of the interior of the blister, the preservative fluid, or the contact lens 64 following treatment (i.e., illumination). Also advantageously, the
35 high-intensity, short-duration pulses of incoherent polychromatic light do not degrade the polyolefin panel

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54, the lid stock 58, or the contact lens 64 contained thereinbetween.

Thus, a terminal sterilization approach is provided for use with a sealed contact lens package that, unlike heretofore known autoclaving and gamma radiation treatment approaches, does not result in degradation of the package being treated or the contact lens contained therein.

Referring to FIG. 4, a side view is shown of the contact lens package 50 of FIG. 3, being suitable for use in the sterilizing chamber (or tunnel) of the apparatus of FIG. 1. Shown are features of the contact lens package 50 of FIG. 3, with the top and the bottom of the package being more clearly identified, and with arrows representing the high-intensity, short-duration pulses of incoherent polychromatic light 66 as they are directed at the blister 52. Similar features bear similar reference numerals to those in FIG. 3.

Referring to FIG. 5, a top view is shown of a contact lens package 70, having a "rectangular" blister 72, and being suitable for use in the sterilizing chamber (or tunnel) of the apparatus of FIG. 1. The contact lens package 70 of FIG. 5 is substantially similar to the contact package 50 of FIG. 3, except that the blister 72 is generally rectangular in shape. The sterilization approach described above in reference to FIG. 3, however, can be employed with similar effectiveness to the contact lens package of FIG. 5. Features shown in FIG. 5 that are similar to features of FIG. 3 bear similar reference numerals.

Referring to FIG. 6, a side view is shown of the contact lens package 70 of FIG. 5, being suitable for use in the sterilizing chamber (or tunnel) of the apparatus of FIG. 1. Shown are features of the contact lens package of FIG. 5, with the top 56 and the bottom 60 of the package 70 being more clearly identified, and with

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arrows representing the high-intensity, short-duration pulses of incoherent polychromatic light 66 as they are directed at the blister. Similar features bear similar reference numerals to those in FIG's 3 and 5.

5 Referring next to FIG. 7, and end view is shown of the sterilizing chamber 18 of FIG. 1. In the variation shown, a single reflector 22 is positioned around a flashlamp 40 and above a parenteral container 12 as it is passed through the sterilizing chamber on, for example, a
10 conveyor belt (not shown). The parenteral container 12 could easily be replaced by an enteral container or a contact lens container as applications demand.

In accordance with the present embodiment, high-intensity, short-duration pulses of polychromatic
15 light in a broad spectrum are directed at the flexible pouch 30 and fitment 32 as they pass through the sterilizing chamber 18. Typically, the intensity of the pulses is from 0.01 J/cm^2 to 50 J/cm^2 , e.g., 0.05 J/cm^2 to 5 J/cm^2 , e.g., 2 J/cm^2 . Advantageously, a high degree of
20 deactivation of microorganisms within the flexible pouch 30, including deactivation of microorganisms suspended within fluid contained in the flexible pouch 30, deactivation of microorganisms at an interface 42 between the fitment 32 and the flexible pouch 30, and
25 deactivation of microorganisms on or within the fitment 32, are effected by the pulses of light.

In some cases, the fitment 32 may not be sufficiently transmissive to permit complete sterilization of the fitment 32 with the high-intensity,
30 short-duration pulses of polychromatic light in a broad spectrum. However, if a sufficiently transmissive material is selected for the fitment 32, and if an appropriate shape and thickness for the fitment is selected, such fitment 32 can be sufficiently sterilized
35 with high-intensity, short-duration pulses of polychromatic light in a broad spectrum. Selection of a

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fitment design suitable for sterilization using high-intensity, short-duration pulses of polychromatic light in a broad spectrum is well within the abilities of the skilled artisan.

5 In accordance with the present embodiment and in the event the fitment cannot be completely sterilized using high-intensity, short-duration pulses of polychromatic light in a broad spectrum, an internal portion of the fitment 32 may be pre-sterilized with heat
10 or gamma-radiation, before being joined to the flexible pouch. An interface region 42, such as shown best in FIG. 2A, at the periphery of the fitment 32, whereat the fitment 32 is joined to the flexible pouch 30, can be treated with the high-intensity, short-duration pulses of
15 polychromatic light in a broad spectrum before and/or after the flexible pouch 30 is filled with fluid, thereby deactivating microorganisms at, in or near the interface region. Such pulses of light preferably have an intensity in the ranges mentioned above, i.e., 0.01 J/cm² to
20 50 J/cm², e.g., 0.05 J/cm² to 5 J/cm², or 2 J/cm² (measured at the interface of the fitment 32 with the flexible pouch 30).

The above-described pulsed light process uses high-intensity, short-duration pulses of polychromatic
25 light in a broad spectrum, i.e., "white" light, to deactivate a wide range of microorganisms, including microbial and fungal spores. During each flash, the intensity of the light is about 20,000 times the intensity of sunlight at the earth's surface, i.e., the
30 "high-intensity" of the light is from between 0.01 J/cm² to 50 J/cm², e.g., 0.05 J/cm² to 5 J/cm² or 2 J/cm², measured at the microorganisms to be deactivated. Each pulse, or flash, of light has a duration of only a fraction of a second (e.g., a "short duration" of from
35 between 0.001 ms to 100 ms, e.g., 0.3 ms).

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The flashes are typically applied at a rate of about 1-20 flashes per second and, for most applications, a few, i.e., 1 through 3, flashes applied in a fraction of a second provide a very high level of microorganism
5 deactivation, or kill. The duration of the light pulses is typically from between 200 and 300 μ s.

The process of the present embodiment uses a technique referred to herein as pulsed energy processing. By storing electrical energy in a high energy density
10 electrical storage capacitor, and releasing it in high-energy, short-duration pulses, high peak power levels are achieved. Such high-peak, power levels of electrical energy can be used to create the high-intensity, short-duration pulses of polychromatic light in a broad
15 spectrum. (Pulsed energy processing is described in the '559, '942 and '235 patents, previously incorporated herein by reference.) The high intensity of these pulses of light results in a unique bactericidal effect not observed when the same energy is provided at low
20 intensity in sustained or continuous wavelength (CW) applications. Although the peak power of each pulse is preferably very high, because of its short duration, the total energy in each pulse is relatively low, and the average power requirement ("wall plug power") is modest.
25 Thus, the process is not only effective, but is economical with respect to energy consumption.

The pulses of light are generated by electrically ionizing a xenon gas lamp, causing it to emit broad band "white" light. A suitable flashlamp
30 system for use with the present embodiment is readily available as Model No. PBS-1 or PBS-2 from Pure Pulse Technologies of San Diego, California, which model utilizes flashlamps, such as are, for example, available as Part No. 01812-525 from PurePulse Technologies, Inc.
35 of San Diego, California. The emitted light pulses have wavelengths of from the far ultraviolet (200 - 300 nm),

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through the near ultraviolet (300 - 380 nm), and visible (380 - 780 nm), to the infrared (780 - 1100 nm). Approximately 25% of the energy distribution is ultraviolet, 45% of the energy distribution is visible, and 30% of the energy distribution of the light is infrared. Because only one to a few, i.e., 1-3, flashes of light are required to achieve microbial deactivation, and can be delivered in a very short period of time, this process can be administered very rapidly, and is usable in high throughput applications.

The light is in the wavelength range classically known as non-ionizing wavelengths, and does not penetrate opaque materials, but is transmitted through many packaging materials and therefore may be used to treat products while in the parenteral and enteral packages described above. The primary effects of treatment, and the main anti-microbial mechanisms, are believed to relate to the rich content of broad spectrum ultraviolet light, and the very high-intensity, short-duration nature of the pulses.

Referring next to FIG. 8, an end view is shown of the parenteral package of FIG. 2 in another variation of the sterilizing chamber 18 (or tunnel) of the apparatus FIG. 1. In the variation shown, a pair of reflectors 22 are positioned around one or more flashlamps 40 and the parenteral container 12, so as to form a tunnel, as the parenteral container is passed through the sterilizing chamber 18 on, for example, a conveyor belt (not shown). The variation shown functions in a manner similar to that in which variation of FIG. 7 functions except that light passing through, or passing by the parenteral container 12 after being emitted from the flashlamp 40, or reflected from an upper reflector 22, is reflected back toward the parenteral container 12 by a lower reflector 22. Advantageously, this variation maximizes the amount of light impinging upon the

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parenteral container 12, thereby maximizing the amount of light passing through the parenteral container 12 to deactivate microorganisms contained therein.

5

EXAMPLE 1

Flexible pouches of polyethylene are fabricated to contain 55 ml of either saline or dextrose. The flexible pouches are inoculated with 1 ml of a *Clostridium sporogenes* spore suspension (6.7 logs per ml.) or a *Bacillus pumilius* spore suspension (8.0 logs per ml.) and mixed. Inoculation control samples are collected from each bag with a sterile syringe in order to quantitate the numbers of viable inoculated spores recoverable from each bag before treatment.

15 The flexible pouches are then placed directly between two reflectors (such as shown in FIG. 8), forming a reflective cavity (or tunnel), and exposed to eight short-duration pulses of high-intensity, broad-spectrum, polychromatic light. After treatment, 1 ml of solution is removed from each bag and plated directly on tryptic soy agar (for the solution removed from the flexible pouches inoculated with *Clostridium sporogenes*) or standard methods agar (for the solution removed from the flexible pouches inoculated with *Bacillus pumilus*). The remainder of each flexible pouch is assayed for sterility by filtration. The experiment is repeated three times for each inoculum/solution combination (total of 12 tests: 3 saline/*Clostridium*; 3 dextrose/*Clostridium*; 3 saline/*Bacillus*; and 3 dextrose/*Bacillus*).

30 *Clostridium sporogene* spores are recovered from the saline filled flexible pouches before treatment at the concentration of 5 logs per ml (or 6.7 logs of spores per flexible pouch), and from the dextrose bags at 4.7 logs per ml (or 6.4 logs of spores per flexible pouch).
35 *Bacillus pumilus* spores are recovered at the concentration of 6.5 logs per ml (or 8.2 logs of spores

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per flexible pouch) in the saline-filled flexible pouches, and at the concentration of 6.2 logs per ml (or 7.9 logs of spores per flexible pouch) in the dextrose solution samples before treatment. After treatment, no viable organisms are recovered from any of the samples, indicating that the treatment is capable of sterilizing the contents of parenteral pouches for each of the inoculum/solution combinations tested. Thus, EXAMPLE 1 achieves a sterility assurance level of greater than 10^{-6} .

10

EXAMPLE 2

Blow/fill/sealed polyethylene containers are filled to various volumes (0.5, 5, 15, and 120 ml) with water-for-injection. *Bacillus pumilus* spores (ATCC 27142), *Bacillus subtilis* strain niger var. *globigii* spores (ATCC 9372), *Bacillus stearothermophilus* (AMSCO commercial preparation) and *Aspergillus niger* (ATCC 16404; containing conididiospores, hyphae and heads) are tested.

Six logs of each organism are inoculated by injection with a small gauge needle. Twelve replicate samples for each combination of organism, container volume, and treatment mode are inoculated. Two of the 12 samples serve as inoculation controls, and the small inoculation puncture is sealed directly with medical grade silicon sealant. Ten of the samples are treated with high-intensity, short-duration pulses of polychromatic light in a broad spectrum, before application of the medical grade silicon sealant in order to prevent shadowing of any sample volume by the sealant.

Two modes of treatment are tested. Containers are treated using a single lamp and reflector (such as shown in FIG. 7) illuminating each container from above with 20 flashes at 1.0 joule per centimeter squared per flash. In a second treatment mode, containers are treated in the reflective cavity (such as shown in FIG.

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4) containing a single lamp with 10 flashes of similar fluence. These 0.5, 5 and 15 ml volumes are tested directly using 20, 20 and 60 ml pour plates respectively. The 120 ml volume samples are tested by filtration. In the single lamp and reflector (SLR) treatment mode, 36 of 40 *A.niger* samples are sterile, and all of the 40 *B.pumilus* spore and 40 *B.subtillus globigii* spore and *B.stearothermophilus* inoculated samples are sterile, i.e., free from viable microorganisms. All samples treated using the cavity treatment mode are sterile, i.e., no viable organisms are recovered from any of the 160 individual samples tested. These results demonstrate that treatment with high-intensity, short-duration pulses of polychromatic light in a broad spectrum can sterilize water-for-injection in polyethylene containers inoculated at the six log level with four resistant strains of microorganisms. Thus, EXAMPLE 2 also achieves a sterility assurance level of greater than 10^{-6} .

Based on the above and numerous other examples, high-intensity, short-duration pulses of incoherent polychromatic light in a broad spectrum have been found to be effective in the sterilization or deactivation of microorganisms in or on pharmaceuticals, food and medical products and devices, and food and medical packaging (See, e.g., the '559, '942 and '235 patents, previously incorporated herein by reference, and U.S. Patent No's 4,464,336; and 5,489,442 (hereinafter the '336 and '442 patents, respectively), both of which are incorporated herein by reference as if set forth in their entirety.) High-intensity, short-duration pulses of polychromatic light in a broad spectrum can thus be used to produce an effective and efficient sterilization method for products, packages, and other target object in situations in which the high-intensity, short-duration pulses of polychromatic light in a broad spectrum can be arranged to access all important surfaces and/or volumes of such

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target object. (Important surfaces and being those surfaces and volumes for which deactivation of microorganisms is desired.) By properly arranging treatment methods and apparatuses, the skilled artisan
5 can assure that the pulses of light will reach the important surfaces and/or volumes to be treated.

Furthermore, and unlike with heretofore known terminal sterilization processes such as autoclaving, key sterilization parameters can be monitored and controlled
10 in accordance with the embodiments described herein. This monitoring and controlling of key sterilization parameters in accordance with embodiments described herein assures a high degree of quality and safety, i.e., a high degree of deactivation, on the target object
15 before the target object is released to and used by an end user.

The sterilization parameters important to achieving sterilization are: (a) the spectral content of each flash, (b) the energy of each flash (or fluence-per-
20 flash in joules/cm²/flash), and (c) the number of flashes delivered.

The importance of the spectral content of each flash is demonstrated by results published in the '559 patent, previously incorporated herein by reference,
25 where it is shown that the ultraviolet content of the pulsed light is of primary importance for the strong antimicrobial effects of pulsed light treatment. This is seen in results of examples in which the ultraviolet content of the flash at wavelengths less than about 320
30 nm are removed by filtration of the light through a quarter-inch thick Pyrex glass filter. Although these results demonstrate that it is high levels of microbial deactivation can still be obtained when wavelengths less than about 320 nm are removed from the treatment flash,
35 it is further seen that much higher fluences and numbers of flashes must be used for the production of

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deactivation effects under these reduced ultraviolet content conditions.

The importance of the energy of the flash (as distinguished from the total energy delivered over some number of flashes) is seen in the results of bacterial and/or fungal spore survival tests in which the ability of different pulsed light treatments to produce sterilization levels of deactivation is evaluated.

10

EXAMPLE 3

The sterilization capabilities of several different pulsed light treatments on *Bacillus pumilus* spores inoculated onto packaging material are shown below in Table 1. *Bacillus pumilus* (ATCC 27142) spores are sprayed onto the inner surface of a multilayer milk box polyethylene/fiberboard/aluminum/polyethylene packaging at 10^7 spores per 1.75cm^2 . Control and treated samples are assayed for surviving organisms by sealing a sterile glass cylinder (3cm diameter) over an inoculated site using a sterile paraffin wax/Vaseline mix (50/50). The treated packaging and attached cylinder are then placed in a sterile petri dish and culture mediums added to fill the cylinder and wet the inoculated surface of the packaging material. Samples are incubated for greater than seven days at 35° and assayed for microbial growth. In one set of samples, a treatment regimen made up of 8 pulses of light] at an incident fluence of $0.5\text{ J/cm}^2/\text{flash}$ (total treatment fluence of 4 J/cm^2) yields surviving organisms in sterilization assays in 6 out of 19 tests (i.e., approximately 1/3 of the samples are not sterilized by this treatment). However, identically inoculated samples yield surviving organisms in: only 1 out of 10 tests when treated with 4 pulses of light at an incident fluence of 0.8 J/cm^2 (total treatment fluence of $3.2\text{ J/cm}^2/\text{flash}$, i.e., 0.8 J/cm^2 less total treatment fluence that with the $0.5\text{ J/cm}^2/\text{flash}$ treatment); and no

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surviving organisms (0 survival) in each of 10 tests when treated with 4 flashes at an incident fluence of 1 J/cm²/flash (total treatment fluence of 4 J/cm²). Thus, at equal or lower total treatment fluence, tests conducted using a higher fluence-per-flash yield dramatically improved deactivation over the test conducted using an equal or higher total treatment fluence, but lower fluence-per-flash.

10

TOTAL TREATMENT FLUENCE (J/cm²)

Fluence per flash (J/cm ² /F)	2.4	2.5	2.56	3.2	4	6
0.3	13/25*					
0.5		11/25			6/19	1/20
0.64			7/25			
0.8				1/10		
1					1/10	
3						2/30

15

20

* Number of samples positive for growth / total number of samples tested

TABLE 1

(It should be noted that the sterility tests described above in EXAMPLE 3 do have an inherent background failure rate due to contamination of samples after treatment. This background false positive rate is associated with posttreatment sample manipulations - such as handling, media filling, etc. - required to complete the assays. Results of control tests using sterile, uninoculated samples treated with high levels of pulsed light and subsequently assayed, suggest the false positive rate is equal to or less than about 1 sample in 10. Therefore the limit of accuracy for the procedures used is approximately 90%, and experimental sample set results with 1 (or less) growth positive samples per 10 total test assays are interpreted as indicating a

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treatment resulting in the maximum detectable level of sterility assurance for the test methodology used.)

EXAMPLE 4

5 The importance of fluence-per-flash is further demonstrated in the results seen in Table 2 where the antimicrobial effects of pulsed light treatments are shown on *Aspergillus niger* (conidiospores, hyphal debris, and sporangia recovered by a crude wash of a mature
10 culture) inoculated by spraying onto the surface of white plastic packaging material. The log survival results are documented for a range of treatments (0.34, 0.53, 0.75, 1, and 1.3 J/cm² per flash) used as a single flash, or after various total numbers of flashes (and therefore
15 various total treatment fluences). When 0.34 J/cm²/flash treatment is performed, the resulting deactivation obtained is relatively constant at about 2 logs survival after about 7 flashes and through treatments ranging up to 40 flashes (40 flashes equals a total accumulated
20 treatment fluence in excess of 13 J/cm²). However, a treatment comprised of a single flash at 1.3 J/cm²/flash is seen to result in no recovered viable organisms for each of three identically inoculated samples tested. Thus, again the treatment consisting of a lower fluence-
25 per-flash, but a dramatically higher total treatment fluence is seen to be far inferior to a treatment consisting of a single blast at higher fluence-per-flash.

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Fluence Per Flash (Joules/sq cm/Flash)						
Total Treatment Fluence (Joules/sq cm)		0.3	0.53	0.75	1	1.3
5	1	3.48	2.23	1.18	0.48	NS
	2	3.38	2.31			NS
	4		1.95	0.60	0.15	NS
	6			0.74		
	7			0.50	0.53	
10	8	2.22	1.47			NS
	12		1.96			NS
	16	1.68	1.23			
	20		1.67			
	24	2.07				
15	32	1.92				
	40	1.73				

NS = No Survivors Detected

TABLE 2

20

Thus, it is seen that the fluence-per-flash used for pulsed light treatment (as opposed to total treatment fluence) significantly affects an overall deactivation efficacy achieved on either bacterial or fungal spores.

The total number of flashes delivered is also of importance. At least one flash clearly must be delivered. In addition, when a product is treated in-flow, such as for the treatment of packaging in a continuous filling machine, such as shown in the '559 patent, or for the treatment of, e.g., running water, some overlapping of the treatment pulses is necessary (because of the digitized or quantitized nature of the light pulses verses the continuous nature of the medic being treated) and some minimum mean number of pulses per unit volume must be delivered and ensured to achieve a desired deactivation efficiency.

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Thus, as shown above, the fluence-per-flash (or flash peak power) is important for achieving deactivation at sterilization levels during pulsed light disinfection. In many applications, the materials, methods, and
5 geometry of the treatment arrangement can be configured to optimize and elevate the efficiency of the pulsed light process and its attendant killing effects.

An example has been reported (U.S. Patent 5,451,367, hereinafter the '367 patent), wherein pulsed
10 light treatment for sterilizing the inner surface of reflective multilayer packaging materials is optimized by choice of materials. A unique and key aspect of this patent is the ability of a reflective inner layer of multilayer packaging material to enhance the pulsed light
15 exposure of microorganisms (and other particles) on the surface of the packaging by providing a mechanism for reflecting light onto the under or down surfaces which are not directly exposed by, and therefore are less accessible to, pulsed light in the absence of such
20 reflective advantages.

A method of significant benefit not apparent from this earlier report (i.e., the '367 patent), and not apparent to the inventors thereof until recently, relates to the capabilities of the arrangement, materials,
25 methods, and geometries described therein to enhance the efficiency and efficacy of the pulsed light treatment process via increases in fluence-per-flash (or flash peak power). For the specific application described in the '367 patent, i.e., the sterilization of the inner surface
30 of reflective multilayer packaging materials, the apparatuses, materials, methods, and geometries discussed provides not only an increased exposure of the shadowed sides of microorganisms and particles, but can also produces an increase in fluence-per-flash without an
35 attendant increase in flashlamp power. This is due to the reflective nature of the light confining cavity

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inherent in some of the geometries attendant to the described apparatuses, materials, methods and geometries. The microbiological benefit of this enhancement in effective fluence-per-flash is described in the
5 discussion presented earlier.

By way of further example, a reflective cavity (such as shown in FIG. 8) constructed of a broadband reflective material and designed to contain a pulsed light source and a transmissive product within a
10 transmissive packaging material can be used to increase the effective fluence-per-flash, and accordingly the microbial deactivation effects of pulsed light treatment. As a result of such arrangement, pulsed light not directly incident on the package is reflected and
15 essentially "recycled" within the reflective cavity to eventually interact with the product. Similarly pulsed light passing through the package and product is reflected and "recycled" within the reflective cavity to again interact with the product. This "recycling" of the
20 pulsed light results in a higher effective fluence-per-flash than would be observed absent the reflective cavity.

Such a reflective cavity, i.e., a reflective cavity exhibiting this "recycling" capability may have
25 many shapes and designs. For example, the reflective cavity could be elliptical in shape with the pulsed light source located at one focus of the ellipse, and the product to be treated located at the other focus. Alternately the reflective cavity could be shaped or
30 patterned to facilitate the return of nonabsorbed light back onto or into the product or package being treated, or to reflect varying fluence levels at various parts of the product or package being treated.

Similarly, the product or package to be treated
35 may be of many types, shapes, materials, and designs. For example, the product may be a solution to be treated

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that is conveyed through the reflective pulsed light treatment chamber in flow in a light transmissive tube, or the product may be air or another gas treated in flow in a reflective pipe or duct. The product may be

5 transmissive to all, a portion of, or none of the pulsed light treatment spectrum employed. Thus, variations on the embodiments described herein may have as their design goal the treatment of the surface of a product (such as the surface of a package), the surface of a package and

10 the product within (such as the surface of a product enclosed within a transmissive package), or the surfaces and volume of a product (such as a transmissive package containing a transmissive product). A wide array of products and cavities are thus contemplated by the

15 inventors named herein.

A common feature, however, of the possible shapes, designs, arrays, and configurations of products, packaging materials, devices, and treatment chambers should preferably be that the apparatuses, methods,

20 materials, and geometries are arranged so as to provide for or permit the reflection of light not initially absorbed within the product, package, etc. in a manner such that such light can be recycled within the cavity to increase the likelihood of the light finally interacting

25 with or being absorbed by the product or package; or microorganisms, chemicals, or contaminants on or in the product or packaging material.

The degree of success or efficiency of the recycling of the initially unabsorbed light will vary

30 with the apparatuses, materials, methods, and geometries employed.

For example, the cavity quotient or Q (the ratio of energy loss per cycle versus the energy stored in the cavity) will vary based upon the pulsed light

35 wavelengths employed, the reflectivity of the cavity

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walls, the ability of the cavity to refocus the light back to useful product surfaces or volume, etc.

However, preferably in all instances the cavity will provide an increase in fluence-per-flash and an
5 enhancement in efficiency by providing for some reutilization of initially unabsorbed light.

For a package and/or product and treatment chamber design that are such that pulsed light within the particular frequency spectrum used for sterilization can
10 reach all the important volumes and surfaces, pulsed light sterilization is dependent upon the spectral content of each flash, the energy of each flash (or fluence-per-flash in Joules/cm²/flash), and the number of flashes delivered. Advantageously, these three
15 parameters are relatively easily and reliably measurable during pulsed light treatment. These three parameters, in accordance with the present embodiments are monitored, controlled, and verified during pulsed light treatment operations. This monitoring, controlling, and verifying
20 proper treatment can then be used for validation of the treatment, i.e., verification that sufficient deactivation is achieved. Specifically, such monitoring, controlling and verifying of proper treatment allows validation of treatment based on measurements of these
25 three parameters alone, as opposed to observation of the packages or products treated for microbial activity following a waiting period.

A key advantage to the use of pulsed light is thus the ability to monitor, control and verify the key
30 treatment parameters, and hence the sterilization effect, in real time and for each package. This importance, i.e., the importance of the ability to control, monitor and verify a sterilization technology, will be appreciated by those familiar with the use and acceptance
35 of sterilization techniques.

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Instantaneous, on-line monitoring and evaluation of each flash of the pulsed light treatment process can be performed at the product, the packaging material, the device or other target object. For

5 transmissive products and packages, the light going through the product and package can be measured both for fluence-per-flash (or flash peak power) and for spectral content. For products and packages that are not

10 transmissive in the wavelengths of interest, reflection off of the product or package can be similarly measured. In both instances the measurement can be performed at one or a multiplicity of sites, or alternatively in a volumetric mode where a large area or volume of the

15 product or package illumination area or volume is sampled through the use of lenses or other mechanisms capable of collecting light over a large angle. In this way pulsed light treatment can be favorably monitored, controlled (through appropriate closed loop feedback control systems), and verified. Thus, not only can each

20 treatment flash be sampled and confirmed as having a minimally sufficient fluence-per-flash and minimally sufficient spectral content, but the fluence-per-flash and spectral content of the light received by the product or package is also monitored in accordance with the

25 present embodiments. This monitoring is performed in an instantaneous, on-line fashion permitting the highest levels of parametric control and verification.

Referring to FIG. 9, a perspective view is shown of a treatment chamber 100, wherein a photodetector

30 is used to measure fluence-per-flash of light emitted from a flashlamp 104, in order to maintain parametric control over sterilization of packages and their contents in the treatment chamber 100. The photodetector 102 along with suitable monitor and control circuitry 106

35 monitors and controls fluence-per-flash, i.e., energy-per-flash, within a prescribed spectral bandwidth, total

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energy over some preselected treatment time, spectral energy within a preselected bandwidth over time, and/or any of a range of other detectable parameters. In a similar fashion the pulse parameters involved in energizing the flashlamp 104, such as current, peak current, current waveshape, voltage, voltage waveshape, and/or any of a range of other pulse parameters may be monitored and controlled by the monitor and control circuitry 106, such as is known in the art. The output from the monitor and control circuitry 106 monitoring both the flashlamp energizing components and parameters, and the resulting flash parameters, are completely describe the operation of pulsed light generation within the treatment chamber 100. Suitable monitor and control circuitry 106 is readily available, such as data acquisition and control cards that can be added to a personal computer 108. Electronic output of the monitor and control circuitry 106, in combination with appropriate programmatic control by the personal computer 108, can be used to monitor, adjust, and document pulsed light treatment. By providing instantaneous electronic signals indicative of parameters related to system operation, in the presence of operation or output outside of a preselected range, feedback circuits in the monitor and control circuitry 106 and programmatically embodied in the personal computer 108 can easily be arranged to adjust system operating parameters and output in accordance with well known feedback/control system approaches.

For example, ultraviolet output from the flashlamp 104 can be coupled to lamp voltage and current operating circuitry in the monitor and control circuit 106 through appropriate feedback/control system circuitry. By monitoring ultraviolet output, system performance can be monitored, adjusted, and maintained each in preselected minima and maxima by coupling this

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information to circuit pulses through appropriate feedback control system circuitry. Similarly, fault detection circuitry within the monitor and control circuitry 106 can be used to summon an operator, shut
5 down the system, or otherwise perform system oversight and alert operations should pulse or output parameters fall below or outside desired levels. In addition, quality control documentation can be performed on-line and in an instantaneous fashion by feeding the electronic
10 signals from operation monitoring systems and output monitoring systems into the personal computer 108 or other computer or electronic storage device.

For pulsed light treatment, a wide range of photodetectors and photooptics may be adapted in a
15 variety of ways to monitor, control, and verify that proper pulsed light sterilization treatment has been achieved. For example, a variety of photooptical methods and detectors are available that can be used to "look at" or interrogate each treatment flash to confirm that the
20 light pulse produced was of the desired intensity, and contained the proper spectral distribution and content. Components for appropriate monitor and control systems are available from a variety of sources and one skilled in the art of photodetector or photooptical systems can
25 design and assemble appropriate systems. For example, surface or volume absorbing calorimeter systems that can be used to monitor the pulsed light fluence per flash or total light output are available from many sources (Gentec, Ophir, Molectron, Digirad, etc.). Similarly,
30 photodetector systems that alone or in combination with appropriate filters or other components are widely available (Hamamatsu, Phillips, EG&G, UDT Sensors, etc.) and can be used to examine the UV content or spectral distribution of the pulsed light flash. The pulsed light
35 can be collected and monitored using a wide variety of means. For example, fiber optic probes, focusing or

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defocusing lenses, integrating spheres, CCD arrays, etc. can be used to collect light from wide or narrow angles or provide spatial resolution of multipoint analysis for the light imaging system. Components or systems for
5 light collecting, handling, monitoring and analyzing are available from many sources; and these components or systems can be designed and assembled by and from a large number of manufacturers or suppliers.

A simple method of quantifying the light
10 signature of a pulsed light treatment flash is shown. A sample of the light flash is collected via a small diameter hole 110, or "pinhole" 110, located in a reflector 112 system used to focus or concentrate the light onto the target object to be treated. The pinhole
15 110 in the reflector 112 transmits light to one or more light sensitive devices (photodetectors 102), such as photometer, a photomultiplier, a calorimeter, a pyroelectric joulemeter, a bolometer, a diode or diode array, or other photosensitive or photodetector system.
20 The photodetector 102 can be used to sample the character (e.g., fluence-per-flash and spectral content) of the treatment light through a variety of means. The light can be "viewed" directly or passed through a sampling port, lens, or likewise apertured, collimated, filtered,
25 focused, defocused, reflected, refracted, or otherwise handled, manipulated, or collected before evaluation.

One, or more photodetectors can interrogate the treatment light from the flash lamp with or without an appropriate filter or filters so that fluence-per-flash
30 and/or spectral distribution can be monitored and controlled.

The signal from the photodetector 102 varies temporally with the fluence-per-flash, and with an appropriate filter or filters such can be specific to a
35 particular portion of the light spectrum. For example, since the ultraviolet fluence-per-flash is generally of

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importance, the photodetector 102 can measure the fluence-per-flash of only the ultraviolet portion of the spectrum through the use of an appropriate ultraviolet bandpass filter. The output of the photodetector 102 can
5 be integrated so as to measure the total ultraviolet energy of the light pulse in the selected bandwidth. This integrated signal is then recorded by either a computer or other means to provide a permanent record of the total energy of the light pulse, and, over time, the
10 entire pulsed light treatment process.

Another key factor is calibration of the measuring system. Many approaches are contemplated for calibration. In accordance with one approach, an ultraviolet calorimeter is placed in the treatment
15 chamber in place of the target object. The calorimeter measures the ultraviolet energy of the light pulse, and is traceable back to international standards. Measurements taken by the calorimeter can thus be compared to measurements taken by the photodetector, so
20 as to calibrate the photodetector to international standards. In a second approach, the light passing through or reflected from the package is measured by the calorimeter.

In general for treatment with pulses of light,
25 packages must be moved through the treatment area in such a manner that the complete package is treated. For transparent packages designed for treatment of products within the package, the process becomes more complex due to internal reflection and refraction of the light as it
30 passes into the package. The following are examples of package transport approaches.

Referring to FIG. 10, a perspective view is shown of several parenteral packages 200, a further variation of the treatment chamber 202 (or tunnel), and a
35 transport approach for moving the parenteral packages through the sterilization chamber. The parenteral

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packages 200 (IV bags), such as the type used to hold intravenous (IV) and parenteral solutions, are treated by hanging them on a ladder-like transport mechanism 204 that carries them vertically through the treatment chamber 202. Pairs of flashlamps 206 are located on each side of the packages 200 as they move through the treatment chamber 202. The treatment chamber 206 includes the flashlamps 206 and reflectors 208 that project light onto the parenteral packages 200. The shape of the reflector 208 are controlled to establish distribution of light as required by the parenteral package 200, i.e., to distribute light onto the parenteral packages 200 such that sufficient fluence-per-flash is directed to each unit volume of the parenteral package 200 and product therein to effect deactivation of microorganisms. The reflectors 208 also increase the Q (the ratio of the energy stored in the cavity versus the energy lost per cycle) of the treatment chamber 202 and allow multiple bounces of light, thus increasing the efficiency and efficacy of the treatment chamber 202. Also shown are photodetectors 210 or other detectors that provide monitoring, control, and verification of the treatment process.

Pulsed light sterilization of IV bags 200 or parenteral solutions may require attention to design, materials and their thickness and other key parameters to assure light can reach and hence sterilize all the important volume and surfaces of the product. Particular attention may have to be paid to special features such as fitments and other normal components on or to the bag which because of stiffness requirements or other considerations may necessitate design or materials selection specifically suited for use with pulsed light while still meeting stiffness requirements, etc.

Another method of treating products is to lay them on a conveyor, such as is illustrated in FIG. 1. A

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section of the conveyor is preferably transparent and in this area packages are treated from the top and the bottom to provide complete coverage.

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CLAIMS

What is claimed is:

1. An apparatus for sterilizing
5 microorganisms at a target object comprising:
a flashlamp system for generating high-intensity, short-duration pulses of polychromatic light in a broad spectrum, and for deactivating microorganisms within the target object by illuminating the target
10 object with the pulses of light having been generated;
a photo-sensitive detector, positioned so as to receive a portion of each of the pulses of light as a measure of an amount of light illuminating the target object, for generating an output signal in response
15 thereto; and
a control system, coupled to the flashlamp system and the photo-sensitive detector, for determining, in response to the output signal, whether the pulses of light are sufficient to effect a prescribed level of
20 deactivation of microorganisms in the target object.
2. The apparatus of Claim 1 wherein the control system further comprises means for monitoring another output signal indicative of a pulse parameter and
25 for further determining whether, in response to the other output signal, the pulse parameter is sufficient to generate pulses of light that effect a prescribed level of deactivation of microorganisms in the target object.
- 30 3. The apparatus of Claim 2 wherein the control system further comprises:
monitor and control circuitry; and
a computer including software.
- 35 4. The apparatus of Claim 2 wherein said control system comprises means for monitoring the other

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output signal, wherein the other output signal is indicative of a pulse parameter selected from a group of pulse parameters consisting of current, voltage, peak current, current waveshape, peak voltage and voltage
5 waveshape.

5. The apparatus of Claim 1 wherein said photosensitive detector generates said output signal, wherein said output signal is indicative of a photo
10 parameter selected from a group of photo parameters consisting of total fluence-per-flash, fluence-per-flash, total energy over time, and energy within a preselected bandwidth over time.

15 6. The apparatus of Claim 5 wherein said control system comprises:
monitor and control circuitry; and
a computer including software.

20 7. The apparatus of Claim 1 wherein said control system includes means for determining, in response to the output signal, whether the pulses of light are of at least a prescribed fluence per flash.

25 8. The apparatus of Claim 1 wherein said control system includes means for determining, in response to the output signal, whether the pulses of light are of at least a prescribed fluence per flash within a prescribed frequency band.

30 9. The apparatus of Claim 1 wherein said means for deactivating includes means for achieving a sterility assurance level of at least 10^{-6} .

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10. The apparatus of Claim 1 wherein said means for deactivating includes means for achieving a sterility assurance level of at least 10^{-3} .

5 11. The apparatus of Claim 1 wherein said flashlamp system includes a reflector at least partially surrounding a flashlamp bulb and said target object for reflecting the pulses of light toward the target object and for reflecting at least a portion of light
10 transmitted through the target object back toward the target object.

 12. The apparatus of Claim 1 further comprising:
15 a reflector positioned proximate to the flashlamp for reflecting the pulses of light toward the target object.

 13. The apparatus of Claim 12 further
20 comprising:
 a hole located in said reflector and in which the photosensitive device is positioned.

 14. A method for sterilizing microorganisms in
25 a target object comprising:
 generating a high-intensity, short-duration pulse of polychromatic light in a broad spectrum;
 deactivating microorganisms at the target object by directing the pulse of light having been
30 generated at the target object;
 receiving a portion of the pulse of light as a measure of an amount of the pulse of light illuminating the target object;
 generating an output signal in response to the
35 receiving of the portion of the pulse of light; and

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determining, in response to the generating of the output signal, whether the pulse of light is sufficient to effect a prescribed level of deactivation of microorganisms in the target object.

5

15. The method of Claim 14 wherein said determining whether the pulses of light are sufficient includes determining whether the pulses of light are of at least a prescribed fluence per flash.

10

16. The method of Claim 14 wherein said determining whether the pulses of light are sufficient includes determining whether the pulses contain at least a prescribed spectral content.

15

17. The method of Claim 14 wherein said deactivating includes achieving a sterility assurance level of at least 10^{-6} .

20

18. The method of Claim 14 wherein said deactivating includes achieving a sterility assurance level of at least 10^{-3} .

25

19. The method of Claim 14 further comprising: reflecting at least a portion of each pulse of light toward the target object.

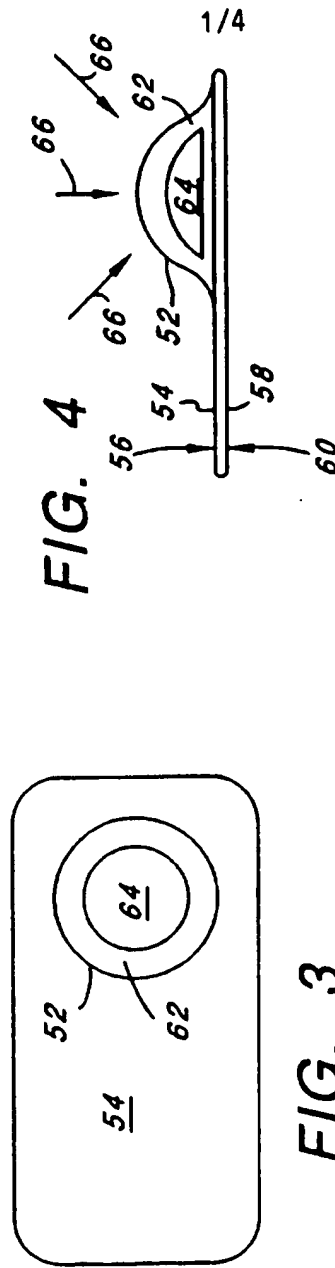
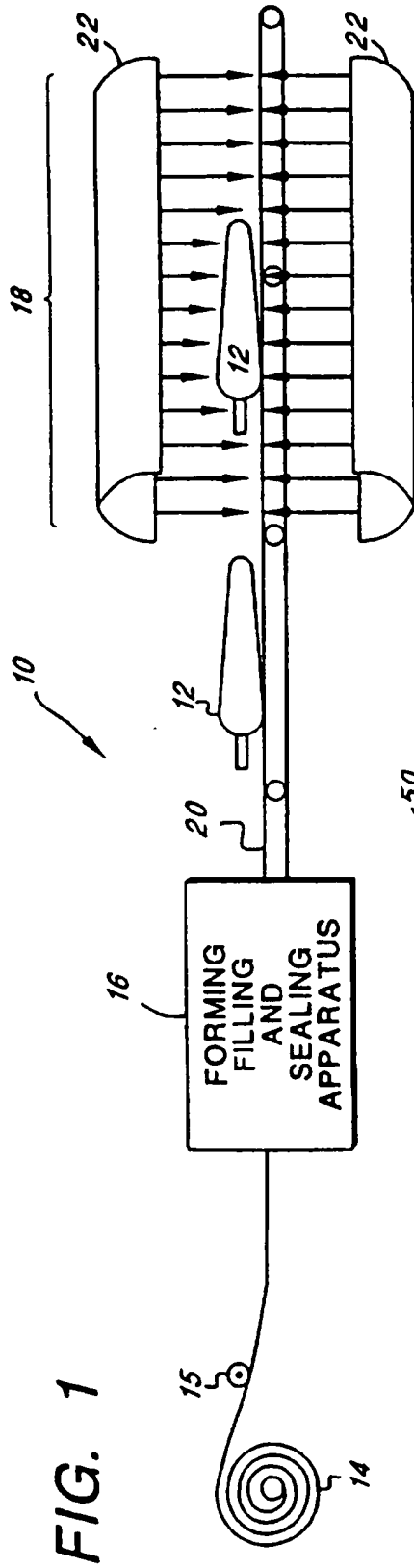


FIG. 5

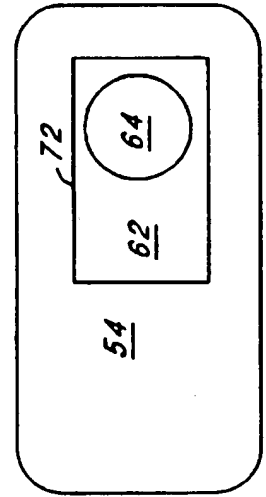
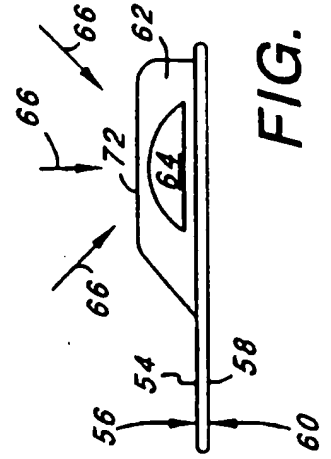


FIG. 6



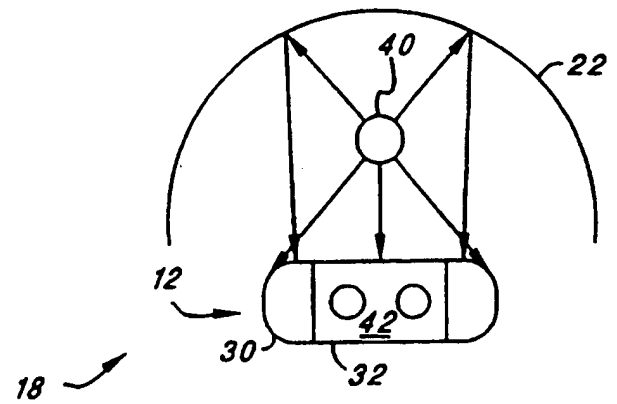


FIG. 7

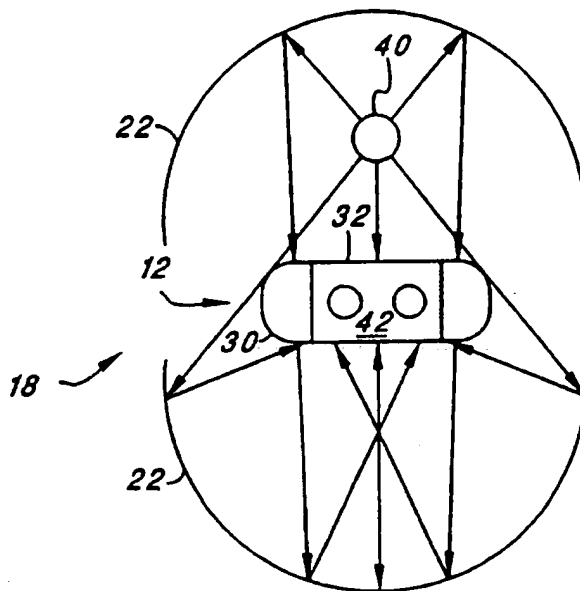


FIG. 8

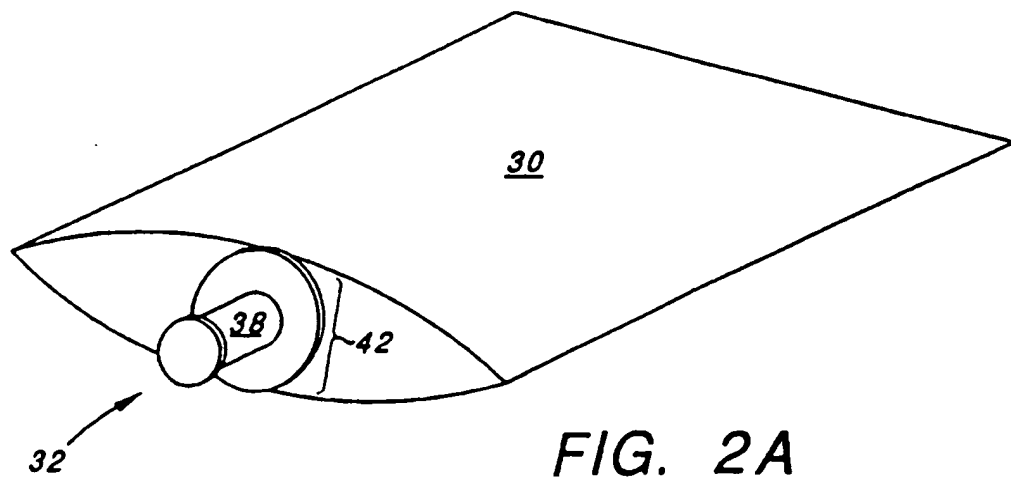


FIG. 2A

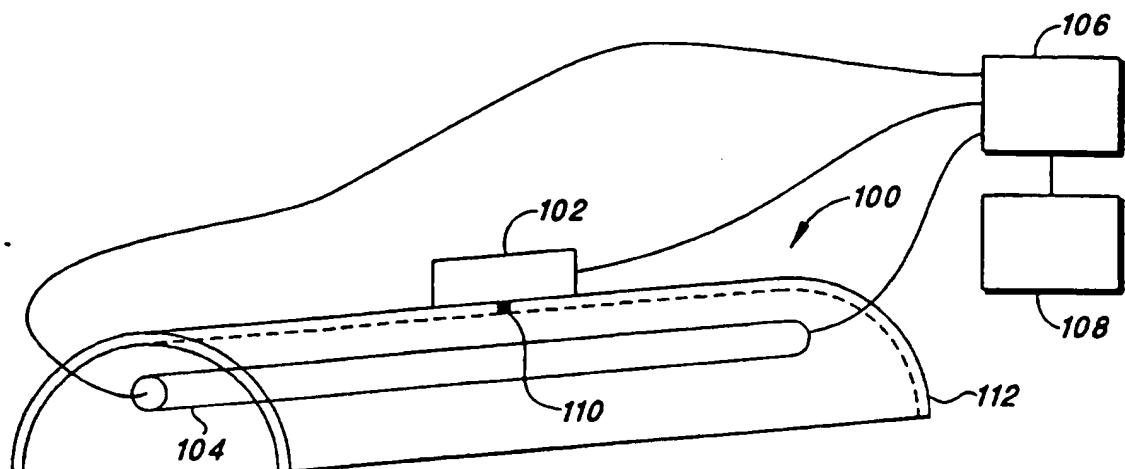


FIG. 9

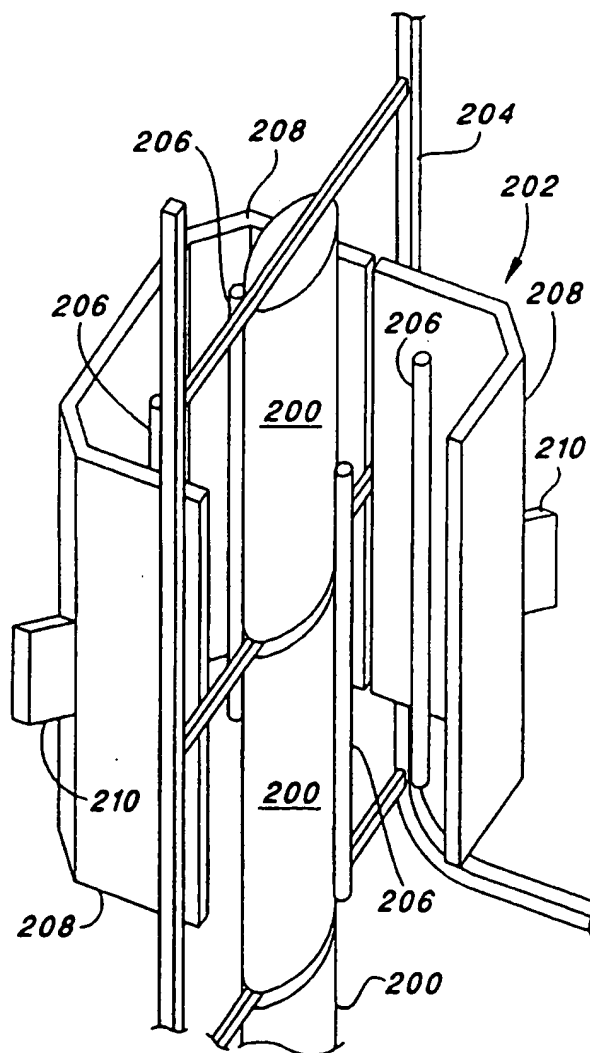


FIG. 10

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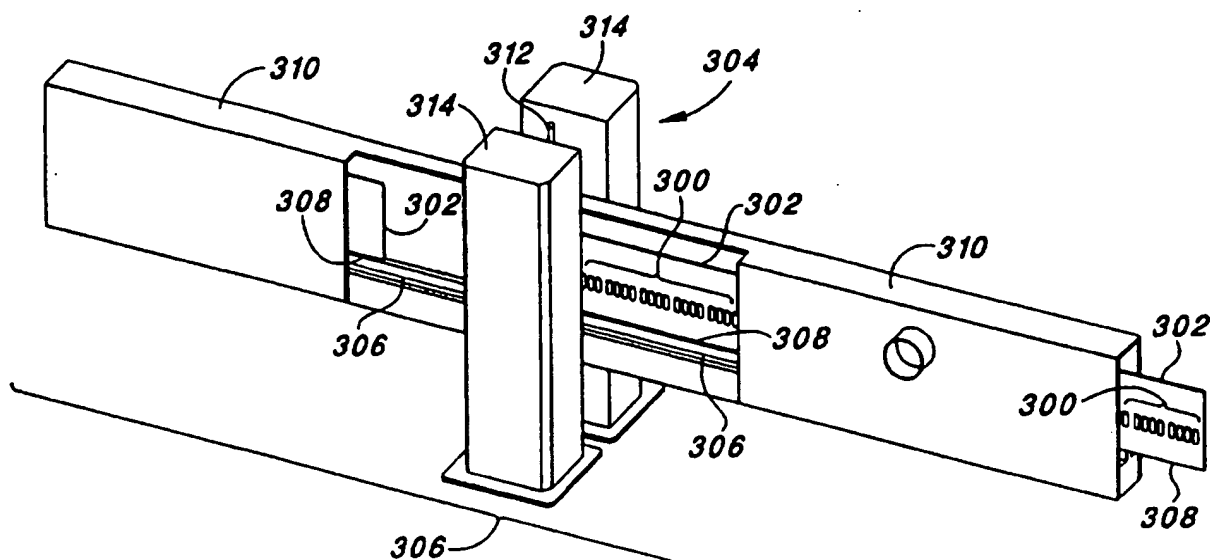


FIG. 11

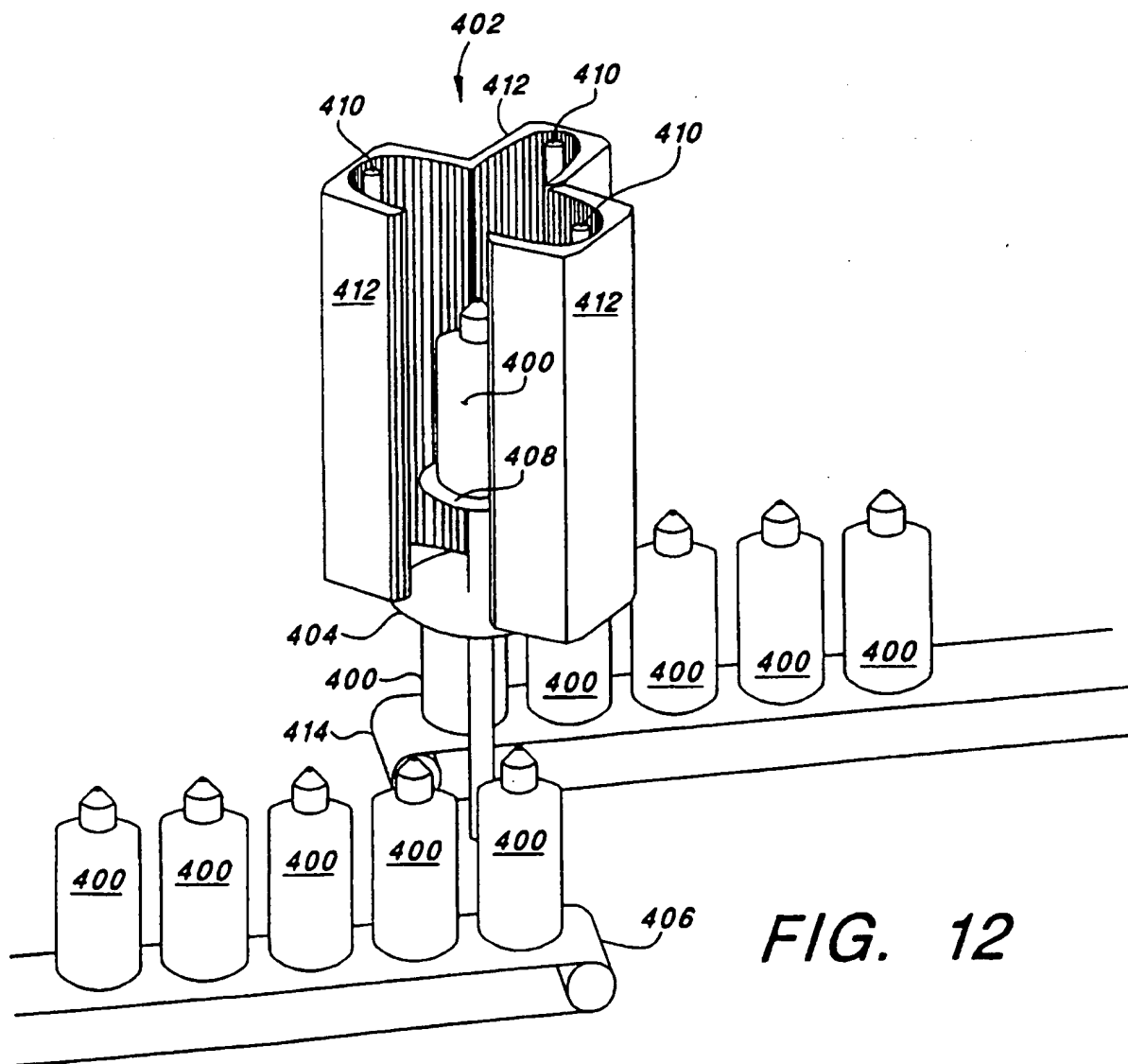


FIG. 12

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 97/07832

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A23L3/28 A61L2/08 B65B55/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A23L A61L B65B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 88 03369 A (MAXWELL LABORATOIRES, INC.) 19 May 1988 see claims 1-3, 9, 10, 21-24, 34-42, 44 & US 4 871 559 A cited in the application ---	1-19
Y	WO 82 01703 A (INTERNATIONAL FARVEFABRIK A/S ET AL.) 27 May 1982 see claims 1-4 ---	1-19
A	FOOD TECHNOLOGY, vol. 49, no. 9, September 1995, CHICAGO, ILL., pages 95-98, XP000530193 JOSEPH DUNN ET AL.: "Pulsed-light treatment of food and packaging" -----	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

5 September 1997

Date of mailing of the international search report

23.09.97

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/07832

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8803369 A	19-05-88	AU 605129 B	10-01-91
		AU 6779287 A	01-06-88
		CA 1292140 A	19-11-91
		DE 3689695 D	07-04-94
		DE 3689695 T	09-06-94
		EP 0290443 A	17-11-88
		JP 1501517 T	01-06-89
		US 4867796 A	19-09-89
		US 4871559 A	03-10-89
		US 4910942 A	27-03-90

WO 8201703 A	27-05-82	EP 0064071 A	10-11-82
		GB 2097919 A,B	10-11-82
		NL 8120415 T	01-10-82
		SE 8204102 A	02-07-82
